

THE OPTIMIZATION OF PROLONGED RELEASE MULTIPARTICULATE TABLETS WITH BETAHISTINE DIHYDROCHLORIDE – Part II

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Abstract

The influence of some formulation factors on the release of betahistine dihydrochloride, an active ingredient freely soluble in water, from multiparticulate tablets with prolonged release was studied.

Prolonged release multiparticulate tablets of betahistine dihydrochloride were prepared by compressing prolonged release granules obtained *via* fluid bed granulation and coating. They were mixed with the suitable excipients (micro-crystalline cellulose -Vivapur type 102 as filler, talcum as lubricant, colloidal anhydrous silica dioxide – Aerosil as glidant).

The fluid bed coating is currently a widely used technique because it allows, among other applications, the coating of crystals or granules with a variety of available polymers, providing modified release systems [1].

In order to obtain a prolonged release drug delivery system, Eudragit[®] RL and Eudragit[®] RS polymers were used as coating agents. The formulation variables studied were the type of the coating polymers and their quantitative ratio, as well as the coating percentages.

The results show that the percentage of polymer used in the tablet formulation has the most significant influence on the drug release.

Rezumat

S-a studiat influența unor factori de formulare asupra cedării betahistinei diclorhidrat, o substanță foarte ușor solubilă în apă, din comprimate multiparticulate cu eliberare prelungită.

S-au obținut comprimate multiparticulate cu clorhidrat de betahistină, prin tehnica comprimării unor granule cu cedare prelungită, obținute prin granulare în pat fluidizat și acoperite cu Eudragit[®], amestecate cu excipienți potriviți (diluante – celuloză microcristalină - Vivapur 102), lubrifianți - talc și glisant - dioxid de siliciu coloidal).

Acoperirea în pat fluidizat este o tehnică larg răspândită, deoarece permite, pe lângă alte aplicații, acoperirea cristalelor sau granulelor cu o varietate de polimeri pentru a furniza un sistem cu cedare controlată [1].

Polimerii utilizați pentru prelungirea cedării au fost Eudragit® RL și Eudragit® RS, iar variabilele de formulare studiate au fost tipul și raportul de asociere dintre polimeri, precum și procentul de acoperire.

Din rezultatele obținute s-a constatat că cea mai mare influență asupra cedării o are procentul de polimer din formularea comprimatelor.

Keywords: betahistine dihydrochloride, coated granules, Eudragit® RS, Eudragit® RL, prolonged release tablets.

Introduction

Over the last years, the use of pharmaceutical preparations with prolonged release has increased, due to their advantages: the decrease of the occurrence of adverse reactions that are caused by exceedingly high levels of active ingredient in plasma, or the lack of therapeutic effect, due to a plasma concentration of active ingredient that is too low. These systems ensure the constant release of the active ingredient in the organism between two administrations, their use allowing a decrease of the frequency of administrations, a significant advantage for the chronic patients [2].

Multiparticulate drug delivery systems have been successfully used for oral controlled drug release. Often, these systems consist of small, spherical or irregular shaped particulates which contain the drug, usually polymer-coated for a prolonged release of the drug, encapsulated or compressed into tablets in order to provide a final dosage form [3, 4].

Polymeric film coatings are often used for achieving a sustained release of an active pharmaceutical ingredient from a formulation because a coated dosage form enables the prolonged and precise release of drug with good reproducibility [5].

Some of the most widely used excipients used in the formulation of prolonged release multiparticulate tablets are polymethacrylate derivatives [2, 5, 6, 7].

The goal of this study was to develop a prolonged release multiparticulate dosage form as tablets with betahistine dihydrochloride and to define some of their pharmaceutical properties (tablet hardness and friability), as well as to study the influence of some of the formulation factors (the type of Eudragit® and coating percentage) on the dissolution profile of the active ingredient from the obtained tablets.

The chosen active ingredient, betahistine dihydrochloride, is a synthetic analogue of histamine [8 – 12]. Betahistine dihydrochloride is indicated in the treatment of vertigo, associated with functional impairment of the vestibular system in the symptoms of Ménière disease. This disease

appears mainly in elderly patients and the treatment is given on a long term; thus an improved compliance is required.

Due to the fact that betahistine dihydrochloride is highly soluble in water and the half-life is short (3 hours) – which leads to frequent administrations (2 to 4 administrations per day, depending on the dosage used – 8 mg/24 mg), a pharmaceutical dosage form that ensures a prolonged and uniform dissolution of the active ingredient is very useful, in the same time reducing the risk of adverse reactions.

Betahistine dihydrochloride is very soluble in water and has a good permeability, therefore this drug can be an appropriate candidate for prolonged release preparations.

For coating the granules we used two types of polymethacrylate polymers: Eudragit® RL and Eudragit® RS. These are methacrylic copolymers with trimethylammonioethyl methacrylate as functional group.

Eudragit® RL and Eudragit® RS are water-insoluble, swellable film formers based on neutral methacrylic acid esters with a small proportion of trimethylammonioethyl methacrylate chloride.

The molar ratio of the quaternary ammonium groups to the neutral ester groups is 1:20 for Eudragit® RL, and 1:40 for Eudragit® RS [6].

Since the quaternary ammonium groups determine the swellability and the permeability of the films in aqueous media, Eudragit® RL forms more permeable films than Eudragit® RS.

The methacrylic polymers Eudragit® RL and RS are insoluble in water, pH independent swelling agents, and the film formed releases the drug by diffusion [6].

The fluid bed coating is currently a widely used technique because it allows, among other applications, crystals or granules to be coated with a variety of available polymers to provide a controlled release system [1].

Materials and Methods

Materials:

Betahistine dihydrochloride (Sifavitor – Italy), Eudragit® RL/Eudragit® RS (supplied by Evonik- Degusa – Germany) used as coating agents, Microcrystalline cellulose - Vivapur 102 (JRS Pharma – Germany) used as filler, Citric acid (Chemopar - Romania) used as antioxidant, Talcum (Luzenac- Italy) and Colloidal anhydrous silica dioxide - Aerosil (Evonik - Germany) used as lubricant-glidant, Ethanol (supplied by Agronad – Romania) used as solvent for the coating solution.

Methods:

A. *The preparation of the multiparticulate tablets*

The granules containing Betahistine dihydrochloride and a part of the total amount of microcrystalline cellulose (Vivapur 102) were obtained by wet granulation into a Fluid Bed Granulator and Dryer (IMA), using water as binder. After drying the granules, the alcoholic polymeric solutions of different types and blends of methacrylic copolymers (Eudragit RL and RS) were sprayed on the granules in a fluid bed coating equipment (Table I). After granulation was complete, the spray was stopped but the fluidizing hot air was continued until the granules were dried.

The rest of the total amount of microcrystalline cellulose, as well as the total amounts of antioxidant – citric acid and glidant and lubricant (talcum and colloidal anhydrous silica dioxide) were added to the resulting prolonged release granules, and the material was compressed in a rotating tablet machine (Manesty XPRES 500 – UK), thus obtaining 300 mg multiparticulate sustained release tablets (Table II).

Table I

The types of polymers, their quantitative ratios and the coating percentage of the prolonged release multiparticulate tablets

Formulation	X ₁ [*]	X ₂ ^{**} (%)
B1	100 : 0	12.50
B 2	100 : 0	20.00
B 3	100 : 0	25.00
B 4	100 : 0	30.00
B 5	0 : 100	12.50
B 6	0 : 100	20.00
B 7	0 : 100	25.00
B 8	0 : 100	30.00
B 9	50 : 50	12.50
B 10	50 : 50	20.00
B 11	50 : 50	25.00
B 12	50 : 50	30.00

*X₁ – ratio of combinations of Eudragit® RL : Eudragit® RS;

**X₂ – coating percentage of the granules

Table II

The formulation of betahistine dihydrochloride prolonged release multiparticulate tablets

Raw materials	B ₁	B ₂	B ₃	B ₄	B ₅	B ₆	B ₇	B ₈	B ₉	B ₁₀	B ₁₁	B ₁₂
	mg/tb	mg/tb	mg/tb									
Prolonged release granules	103	113.2	120	126.8	103	113.2	120	126.8	103	113.2	120	126.8
Microcrystalline cellulose 102	192.16	181.96	175.16	168.36	192.16	181.96	175.16	168.4	192.16	181.96	175.16	168.36
Talcum	3.84	3.84	3.84	3.84	3.84	3.84	3.84	3.84	3.84	3.84	3.84	3.84
Colloidal anhydrous silica dioxide	1	1	1	1	1	1	1	1	1	1	1	1
Ethanol*	83	131.63	164.54	197.45	83	131.63	164.54	197.5	83	131.63	164.54	197.45
Purified water*	8	14	16	18	8	14	16	18	8	14	16	18
Total	300	300	300									

* removed during processing

The individual weight of the tablets obtained were of approximately 300 mg, each tablet containing 32 mg betahistine hydrochloride as active pharmaceutical ingredient.

B. The evaluation of the multiparticulate compressed tablets

Hardness and Friability

The tablet hardness parameter was determined on 10 tablets of each formulation, using the Tablet Hardness Tester (TABLET TESTER 8 M - Dr.Schleuniger, Switzerland) in accordance with the provisions of the Romanian Pharmacopoeia 10th Ed. and the European Pharmacopoeia, 7th Edition [13].

The determination of the friability was performed on 20 tablets of each formulation, using a Friabilator (EF-2 – Electro Lab, India) in accordance with the requirements of the Romanian Pharmacopoeia 10th Ed.

***In vitro* release studies**

The dissolution test has been carried out in accordance with the Romanian Pharmacopoeia 10th Ed. and the European Pharmacopoeia, 7th Edition – method 1, using SR 8 Plus Dissolution Testing Station (Hanson Research – USA).

The test was performed under the following conditions:

- dissolution medium: distilled water;
- medium volume: 900 mL;

- temperature: $37 \pm 0.5^\circ \text{C}$;
- speed rotation: 75 rpm;
- test duration: 12 hours.

The samples were collected at predetermined time intervals (1, 2, 3, 4, 5, 6, 8, 10, 12 hours) and the assay of betahistine dihydrochloride has been performed within European Pharmacopoeia 7th Ed. conditions. At each time interval, samples of 50 mL were withdrawn from the dissolution media, immediately filtered through a 0.45 μm filter and replaced with fresh media to maintain a constant volume during the experiment.

The assay was performed spectrophotometrically under UV light, at $259 \pm 2\text{nm}$ wavelength.

The *in vitro* studies were performed in triplicate.

Results and Discussion

Pharmacotechnical parameters

The results obtained after performing the tests for tablet hardness and friability are shown in Table III.

Table III

The influence of the type of Eudragit® (%) and concentration of Eudragit® coating solution, on the hardness and friability of the multiparticulate tablets

Formulation	Hardness [N]	Friability [%]
B1 (12.5% EUDRAGIT® RL)	58.3	0.68
B2 (20% EUDRAGIT® RL)	45.4	0.84
B3 (25% EUDRAGIT® RL)	44.2	0.91
B4 (30% EUDRAGIT® RL)	41.3	1.03
B5 (12.5% EUDRAGIT® RS)	57.21	0.69
B6 (20% EUDRAGIT® RS)	49.6	0.79
B7 (25% EUDRAGIT® RS)	47.5	0.88
B8 (30% EUDRAGIT® RS)	43.1	1.45
B9 (12.5% EUDRAGIT® RL+ EuEUDRAGIT® RS)	58.2	0.70
B10 (20% EUDRAGIT® RL+ EUEUDRAGIT® RS)	46.2	0.82
B11 (25% EUDRAGIT® RL+ EUEUDRAGIT® RS)	44.6	0.89
B12 (30% EUDRAGIT® RL+ EUEUDRAGIT® RS)	42.3	1.32

The values obtained show that the B1, B5 and B9 formulas, which are produced with 12.5% polymethacrylate polymers, had a greater hardness and a lower friability.

The friability of the B1-B3, B5-B7, B9-B12 formulations was less than 1%, which is a good value [13]. The friability of the B4, B8, B12 formulas was more than 1%. For all the studied tablets, the hardness was over 40N.

Regarding the percentage of polymethacrylates in the tablets, the ones with an increased quantity of polymethacrylates had a lower resistance than the ones with a lower quantity of polymethacrylates.

***In vitro* release study of betahistine dihydrochloride**

The mean values of the 3 determinations for each formulation are shown in Table IV.

Table IV

The influence of the type of Eudragit® (%) and concentration in Eudragit® coating solution, on the *in vitro* release of betahistine dihydrochloride from the multiparticulate compressed tablets

Percentage of betahistine dihydrochloride released from the multiparticulate tablets at different time intervals (%)									
	1 h	2 h	3 h	4 h	5 h	6 h	8 h	10 h	12 h
B ₁	55.95	67.5	69.7	75.21	86.24	92.57	98.99	100	100
B ₂	51.51	64.54	69.25	72.48	87.57	93.47	97.57	100	100
B ₃	47.38	62.75	67.24	71.54	78.58	88.25	91.46	100	100
B ₄	44.89	58.74	61.57	67.54	74.57	79.54	86.32	100	100
B ₅	45.57	62.47	64.28	70.25	82.21	86.54	94.21	100	100
B ₆	43.37	61.55	64.27	69.71	74.21	79.89	88.32	97.14	100
B ₇	36.28	55.14	58.64	64.21	67.98	76.24	86.21	95.14	100
B ₈	36.14	48.57	52.47	56.59	62.47	69.51	76.22	92.55	100
B ₉	47.22	62.88	66.21	75.24	83.23	88.57	94.55	100	100
B ₁₀	46.15	62.94	65.11	71.24	75.21	87.24	90.12	100	100
B ₁₁	44.95	57.24	61.57	68.22	74.21	82.28	88.47	99.14	100
B ₁₂	39.81	52.47	55.41	63.24	68.74	76.25	83.54	96.51	100

The release profiles of betahistine dihydrochloride from the formulated experimental prolonged release tablets are shown in fig. 1.

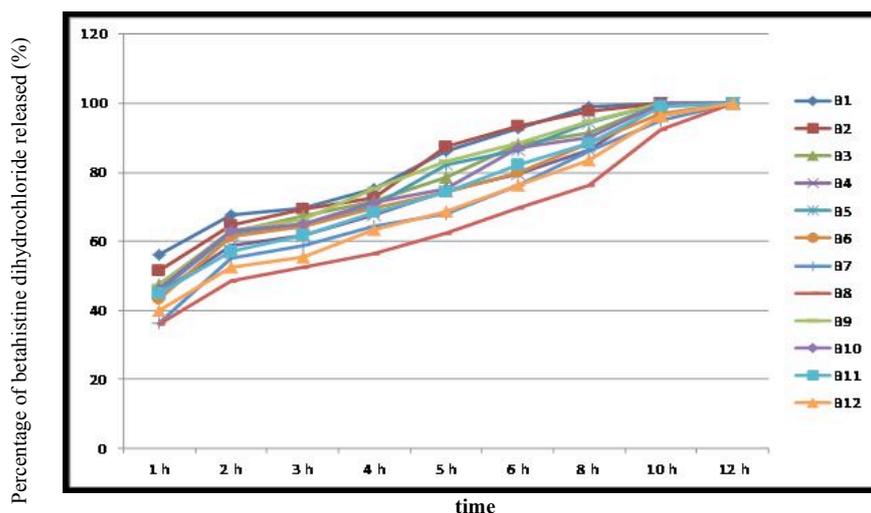


Figure 1

Release profiles from the studied prolonged release tablets

These results show that the increase of the Eudragit® percentage within the formulation has a significant influence on the prolongation of the betahistine hydrochloride release of from the tablet.

The formulas B1-B4, which are produced using Eudragit® RL, developed a faster dissolution profile, compared with formulas B5 to B8, which are produced with Eudragit® RS.

This behaviour could be explained by the fact that Eudragit® RL has a molar ratio of quaternary ammonium groups to neutral ester groups higher than the molar ratio of quaternary ammonium groups to neutral ester groups in Eudragit® RS, which means that the films formed with Eudragit® RL are more permeable than the films formed with Eudragit® RS.

The best results were obtained in the case of formula B8, where the prolongation of release was less than 80% in 8 hours.

A ratio of 50:50 of the two Eudragit® types led to intermediary dissolution profiles.

By comparing the Eudragit types, in the formulas with the same coating percentage, it could be observed a delay in the release of the active ingredient, ranging from about 10% in the first hour to about 90% after 8 hours.

Conclusions

In this study, we showed the effect of the variation of the ratios of polymers Eudragit® RL and RS on the release of betahistine

dihydrochloride from multiparticulate compressed tablets, in order to attain the sustained release property of the granules formulated in the multiparticulate tablet, using a fluid bed granulation-coating technique.

We found that the increase of the percent of Eudragit polymer used as a coating agent had a significant influence on the prolongation of the betahistine dihydrochloride release from the tablet.

Due to the low permeability of Eudragit® RS, the formulation with the highest coating percentage of this polymer had a delay in the release process, lower than 80% after 8 hours.

In conclusion, the types and the blends of polymers represent an important formulation factor for the sustained release from tablets of betahistine dihydrochloride, a highly water soluble drug.

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